REMARKS

This invention is directed to methods of treating cardiac fibrosis by the administration of quinazolinones. The specification and examples demonstrate the efficacy of halofuginone, a species of quinazolinone, for inhibition of the pathological progression of cardiac fibrosis.

Reply to the Examiner's Rejections:

The Examiner has rejected claims 24, 25 and 28 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,449,678 ("Pines") and further in view of Ramieres et al., J. Mol. and Cell. Cardiol., 1998, abstract, 30(3), pp. 475-83 ("Ramieres") and /or Crawford et al., Circulation Res. 1994, abstract, (4), pp. 727-39 ("Crawford"). According to the Examiner, Pines teaches the use of quinazolinones for treating and preventing fibrotic disorders such as myocardial fibrosis by inhibiting collagen type I synthesis. The Examiner further contends that Pines teaches that halofuginone inhibits collagen type I synthesis at the transcriptional level, regardless of the tissue or animal species. Applicants respectfully disagree.

The present application relates to the prevention and/or treatment of cardiac fibrosis by the administration of quinazolinone derivatives such as halofuginone, as well as pharmaceutical compositions for the administration of such quinazolinone derivatives to a patient. The specification, in particular Example 5, demonstrates the efficacy of halofuginone *in vivo* for the inhibition of the pathological processes of cardiac fibrosis and hence for both the treatment and prevention of cardiac fibrosis. The specification describes a large number of different mechanisms which may be responsible for the *in vivo* efficacy of halofuginone and

related compounds, including inhibition of collagen α1(I) gene expression and hence reduction in collagen type I synthesis; inhibition of collagenase type IV production; inhibition of H19 gene expression; decreasing the release of cytokines IL-1β and TNFα; overall regulation of ECM (extracellular matrix) deposition and remodeling; and inhibition of integrin expression. *See* e.g., page 19, lines 1-10; Examples 2, 3 and 4. Thus, inhibition of collagen type I synthesis is only one of many different potential targets of Halofuginone for treating and/or preventing cardiac fibrosis.

Both structurally and functionally, cardiac tissue is a unique tissue. Structurally, it is neither typical of striated muscle nor typical of smooth muscle but rather shares attributes of both types of muscle. Functionally, it is unique in that it must contract in a predetermined carefully orchestrated fashion in order to accomplish its function, and even minor structural damage can impede its proper function. What might constitute a survivable level of damage or loss of functionality in almost any other tissue type (certainly in any other muscle type) can be life threatening in the case of cardiac function. *See* page 27, lines 6-19. Thus, unlike the cited prior art, the present specification demonstrates the efficacy of halofuginone as a treatment and/or suitable preventive medicament for this highly unique tissue.

The instant application also specifically distinguishes Pines, and in particular, addresses the difficulties in predicting the *in vivo* effects of halofuginone based on results of *in vitro* experiments:

> However, the *in vitro* action of Halofuginone does not always predict its *in vivo* effects. For example. Halofuginone inhibits the synthesis of collagen type I in bone chondrocytes *in*

> *vitro*, as demonstrated in [Pines] U.S. Patent No. 5,449,678. However, chickens treated with Halofuginone were not reported to have an increased rate of bone breakage, indicating that the effect is not seen *in vivo*. Thus, the exact behavior of Halofuginone *in vivo* cannot always be accurately predicted from *in vitro* studies.

Page 9, lines 1-7.

Pines describes *in vitro* tissue culture experiments to determine the effect of halofuginone on skin fibroblasts and chondrocytes. Pines does not, however, demonstrate that halofuginone would be effective in an *in vitro* (or *in vivo*) tissue culture assay with cardiac or other similar types of cells. As stated in the present application, results obtained with *in vitro* experiments using fibroblasts are not necessarily predictive of the behavior of cardiac cells after contact with halofuginone *in vivo*.

A reference cited to reject claims based on § 103(a) obviousness must not only suggest the treatment of cardiac fibrosis with halofuginone, it must also provide a reasonable expectation of success that administration of halofuginone to an individual suffering from the cardiac fibrosis would be successful in treating or preventing the disease. Pines is a general approach. That is insufficient. A general approach amounts only to an "obvious-to-try" situation -- a standard for obviousness that has been repeatedly rejected. *Gillette Co.* v. *S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed.Cir. 1990) ("An 'obvious-to-try situation' exists when a general disclosure may pique the scientist's interest ..."). Pines, based merely on its effects on avian skin fibroblasts and chondrocytes, does not provide a reasonable expectation of success that administration of halofuginone to a patient would effectively prevent and/or treat cardiac fibrosis. Therefore, Pines cannot amount to a teaching that the use of Halofuginone can

prevent and/or treat cardiac fibrosis *in vivo*, as disclosed and taught in the present application. Accordingly, the present invention is not obvious in view of Pines taken alone or in view of Ramieres and Crawford.

Applicants request that the Examiner consider the foregoing remarks and allow this application to issue. A telephonic interview with applicants' representative is kindly requested if it would help the Examiner in placing the claims in condition for allowance.

Respectfully submitted,

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